IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No: 20780-0006

Applicant(s):	Jeffrey W. RUBERTI *et al.*	Confirmation No.: 9743
App. No.:	10/771,852	Examiner: K. Egwim
Filing Date:	February 4, 2004	Group Art Unit: 1796
Title:	SYSTEMS AND METHODS FOR CONTROLLING AND FORMING POLYMER GELS	

DECLARATION OF GAVIN BRAITHWAITE

I, Gavin Braithwaite, do hereby declare as follows:

1. I received my Ph.D. in Chemical Engineering from Imperial College of Science, Technology and Medicine, London, England in 1997. I have been engaged in the study of polymers for about 15 years. I have authored or co-authored 11 peer-reviewed articles and two book chapters. I am the Vice President of Research at Cambridge Polymer Group, and a named inventor on the captioned application. A copy of my *curriculum vitae* accompanies this declaration.

2. I provide this declaration to explain the nature of the problems (both generally known and not generally known) encountered in soft tissue replacements in the orthopedics field, the prior art attempts at solving these problems, the differences between our invention and the prior art, and the advantages provided by our invention over the prior art. Soft tissue replacements are used in a wide variety of contexts. Notable examples are in the spine, the heart and the breast. The independent claims that I focus upon here are:

> **135. (New)** An injectable thetagel solution for injection into a body space, wherein the injectable solution is obtained by a process comprising the steps of:

dissolving polyvinyl alcohol (PVA) molecules in a first solution to form a PVA solution, wherein the first solution has a Flory interaction parameter (chi value) that is not sufficient for gelation;

contacting the PVA solution with a second solution in a controlled manner, wherein after the contacting the combination of both solutions has a Flory interaction parameter (chi value) that is sufficient for gelation, and thereby forms an injectable thetagel solution; and

maintaining for a period of time the injectable thetagel solution at a temperature such that it is in a workable state, wherein the injectable thetagel solution can be injected into a body space, and therein gel *in situ* after the injection to form in the body space a polymer hydrogel that has physical crosslinks between PVA molecules, wherein the polymer hydrogel is formed without chemical crosslinkers, irradiation or thermal cycling, and wherein the polymer hydrogel can fill the body space.

146. (New) A polymer hydrogel formed within a body space, wherein the polymer hydrogel is obtained by a process comprising the steps of:

(I) injecting an injectable thetagel solution into a body space, wherein the injectable thetagel solution is produced by:

(A) dissolving polyvinyl alcohol (PVA) molecules in a first solution to form a PVA solution, wherein the first solution has a Flory interaction parameter (chi value) that is not sufficient for gelation;

(B) contacting the PVA solution with a second solution in a controlled manner, wherein after the contacting the combination of both solutions has a Flory interaction parameter (chi value) that is sufficient for gelation, and thereby forms the injectable thetagel solution; and

(C) maintaining for a period of time the injectable thetagel solution at a temperature such that it is in a workable state;

and

(II) allowing the injectable thetagel solution to gel *in situ* after the injection to form in the body space a polymer hydrogel that has physical crosslinks between PVA molecules, wherein the polymer hydrogel is formed without chemical crosslinkers, irradiation or thermal cycling.

3. In this declaration, I discuss the spine. Slide 1 depicts a normal human healthy disc. The intervertebral disc provides load-support while allowing flexibility and rotation. By way of analogy, the disc acts like a car tire to support a high dynamic load using a compressible fluid/gas (the nucleus for the spine, or air for a tire) by confining it in a flexible wall (the annulus for the spine, or the tire wall for a car tire).

4. A healthy nucleus is a collagenous hydrogel that is not sufficiently strong on its own to support the weight of the body. However, on its own the annulus also does not possess the right mechanical properties to flex and bear a load. The composite structure of the disc, with the nucleus surrounded and supported by the annulus, allows the disc to operate correctly. See Slide 2.

5. As the disc ages, or becomes damaged, it is often the nucleus that is impacted first, either suffering dehydration, or becoming extruded (herniated) out of the annulus. Loss of height almost inevitably results, changing the biomechanics of the spine and resulting in pain and osteophyte formation, further reducing mobility and initiating the "degenerative cascade". Loss of volume, or a dehydration of the nucleus results in compromised biomechanics and the onset of the degenerative cascade. See Slide 3.

6. Current surgical treatments range from conservative therapies such as physical therapy and drugs in the form of painkillers and surgery. The majority of patients are well treated by conservative approaches but a significant subset require more invasive surgeries. Removal of material to relieve pressure on nerve roots (laminectomy and discectomy) is successful in the short term but the removal of material probably accelerates the degenerative process. Vertebrate fusion is the current standard which works by preventing motion in the affected segment, but this approach is invasive, permanent, results in overall loss of motion and may accelerate degeneration in adjacent segments by transferring motion forces and load. See Slide 4.

7. There are emerging technologies for total disc replacement, but these are even more invasive and complex, and the long term prognosis is not clear. Currently, the Raymedica family of devices is widely used outside of the US. However, these devices are implanted as dehydrated devices which, although shrunk before implant, still require large incisions to allow insertion which compromises the integrity of the joint space. These devices have been prone to expulsion through the surgical incision, and also have problems with uneven loading of the vertebral end-plates that ultimately results in subsidence. These implants cannot fully and evenly transfer load from the end-plate to the annulus in the manner that the natural nucleus operates. See Slides 4 and 5.

8. Due to the limitations of fusion and disk replacement, other approaches have been under development. What has been needed is an approach that mimics the load-distribution operation of the natural nucleus. Since the natural nucleus is a hydrogel, an injectable hydrogel that can fully fill the nucleus space is ideal. There are a number of products in development that attempt to address the issue of a biocompatible, permanent, injectable hydrogel, but none do so completely. All of the systems identified in Slide 6 use chemical crosslinkers except for the BST-disc and the Gelifex system, which are "phase change" materials that rely solely on the surrounding conditions to form a gel at all times. Since phase change is a thermodynamic system,

they are not permanently crosslinked and therefore could suffer from long-term instability *in vivo*.

9. In summary, prior to the claimed invention, the field employed materials that used chemical cross-linkers that can create bio-incompatible reaction products, required irradiation and/or thermal cycling, or would by unstable due lack of physical cross-linking (*e.g.*, bonding). These limitations were solved for the first time by the claimed invention, and advantageously employ useful characteristics of polyvinyl alcohol (PVA). PVA is a proven biomaterial. See Slide 7.

10. PVA is formed by the hydrolysis of PVAc poly(vinyl acetate). The PVA chain is a string of carbon atoms with either two hydrogens or one hydrogen and an oxygen-hydrogen group (-OH, or hydroxyl group). This hydroxyl group gives PVA its unique abilities in solution. PVA bonds to itself in water systems through a hydrogen-bond. See Slide 8.

11. How PVA is employed according to the invention involves polymer thermodynamics. Whether a polymer molecule dissolves in a solvent or not is governed by two main parameters, the affinity of the polymer molecule to the solvent, described as the heat of mixing, and the amount of disorder in the system (the entropy of mixing). The former describes whether the polymer molecule is "compatible" with the solvent chemically, and the latter describes if the molecule is highly structured in its natural state. Thus, the free energy of the system describes the energy gained or lost by making the solution. This parameter can be described by the relative solution concentrations and molecule numbers, and the Flory interaction parameter (chi), which characterizes the chemistry of the solution. The Flory interaction parameter describes how the energy of the system changes per molecule added with all other parameters held constant. The chemical potential of a molecule is the derivative of the free energy with respect to the number of molecules. As a result a negative chemical potential requires energy to have been input and thus is "unfavorable" and cannot happen

spontaneously. A positive chemical potential indicates that the new solution is energetically favorable and will happen spontaneously. See Slides 9 and 10.

12. Slide 11 provides an explanation of a theta solvent. A theta solvent refers to condition that balances the competition between the polymer segments and the solvent. It is energetically just as favorable for a polymer segment to be next to another polymer segment as to the solvent and therefore the polymer chain is neither extended nor relaxed. In the context of PVA hydrogels according to the claimed invention, this transition is used to control how the polymers interact, forcing a hydrogel to form in a "poor" solvent and then allowing the hydrogel to fully hydrate in a "good" solvent.

13. Slide 12 provides phase diagrams. The phase diagram of water indicates that above the red line water is either solid (ice) or liquid (water). For the binary (two-component) phase diagram above the red line either the sucrose is fully or partially dissolved. However, the system is only pure liquid to the left of the green line. To the right of the green line exists a phase where the sucrose is dissolved in the water (syrup) and the sucrose exists as a solid. For the polymer-solvent mixture, a solution that is below the red line is fully dissolved in the solvent. This solvent can be one, or a combination of solvents. A solution above the line is unstable since the polymer is only partially soluble. There therefore exists two concentrations (roughly described by the red line) in which the polymer can exist. See figure 2 of the captioned application.

14. Slide 13 depicts phase separation with a 'kitchen table' example. Phase separation can happen spontaneously when the two components are immiscible (i.e. incompatible). This incompatibility can be influenced by the presence of other ingredients. Slide 14 depicts a phase separation phenomenon in the context of polymers. If solvent conditions change, the polymers can come out of solution and form a solid ("crash out"). Thus, solution conditions govern how the polymer interacts with itself and the solvent, and macroscopically whether the solution separates/precipitates/curdles, or not. Another 'kitchen table' example which directly relates the solvent quality to the behavior of the polymer (a protein in this case) involves

the addition of vinegar to milk. Vinegar causes casein (a natural protein found in milk, and is a polymer) to curdle and thus separate from the whey. See Slide 15.

15. Returning to hydrogels, phase separation takes time to evolve in a system that undergoes controlled phase separation as compared to precipitation. The graph presented in Slide 16 is based on rheological data for 15% PVA in deionized water, with 28% polyethylene glycol (PEG). Both percentages are relative to the water content in the solution. The solution is initially at 90 °C but is rapidly cooled at t=0 to 40 °C. The phase angle returned from a small amplitude oscillatory shear experiment is defined as the phase angle, delta, where $\tan(\delta)=G''/G'$ where G' is the elastic modulus and G" is the viscous modulus. $G^*=(G'^2+G''^2)^{0.5}$ is the magnitude of the complex modulus. Delta is generally considered to indicate the relative viscosity-to-elasticity. Thus, the rheology indicates that formation of a hydrogel through gelation (the solution is predominantly elastic) only occurs after about 25 minutes at 40°C. Corroborating this information, the images along the bottom are taken from a simulation and show the development ("coarsening") of the structure with time. There is a time involved in the phase separation that allows manipulation of the material once the solution conditions change. As summarized in Slides 17 and 18, structure can be imposed on PVA using phase separation, driven by the solution conditions. Almost unique to PVA, this structure can be "locked-in" by allowing the temperature to fall below the crystallization temperature of the PVA crystals.

16. The surgical procedure outlined in Slide 19 provides a method for introducing a PVA hydrogel in a minimally invasive manner. The example outlined on this slide injects the material through the annulus wall, but the disc itself is exposed for demonstration purposes. From left to right: The material is injected through a standard needle (16G) using a conventional sterilized syringe. Since the only incision in the disc is a needle stick a second needle is provided to provide pressure relief. The syringe can be seen in a porcine model in the second image, with an interoperative fluoroscopic image of the procedure alongside. In the final images the disc has been dissected to show the characteristic white gel manufacture by this method. The gel is clearly kidney

shaped and conforms to the shape of the cavity it was injected into. The method outlined here allows the percutaneous injection of a PVA-based totally biocompatible hydrogel into a disc space where it totally fills and conforms to the space that the natural nucleus pulposus previously occupied.

17. Slide 20 shows a sequence of still images taken from a video of a bench-top demonstration of the primary concept of injecting a PVA solution into a body cavity for subsequent gelation into a viscoelastic hydrogel. The images shown represent an experiment on a porcine intervertebral disc. From left to right, and top to bottom:

(1) an overview of the disc shows the top end-plate, and the spinal processes of the porcine vertebral unit

(2) a closer zoom shows the end-plate and the spinal canal

(3) The end-plate is removed to allow access to the natural nucleus pulposus

(4) A plexiglass sheet is placed on top of the disc to allow visualization. Note white kidney-shaped annulus and the space remaining after removal of the nucleus

(5) A 16G needle is inserted into the disc. A small blob of hydrogel is visible at the tip

(6) The PVA solution with gellant is injected into the space beginning to fill the nucleus space. Note that the solution is already translucent indicating that the physical crosslinks are beginning to form even though the solution is still injectable

(7) Further material is injected. Note that the solution is fully filling the cavity

(8) Injection is finished and the solution has fully flowed into every corner of the space available

(9) After approximately 10 minutes the plexiglass is removed and the now-gelled hydrogel is peeled out of the space

(10) the hydrogel clearly has formed a three dimensional shape that matches that of the nucleus space it was formed within.

(11) The final hydrogel after removal has the shape of the nucleus space and is a viscoelastic solid while being approximately 85% water for this formulation.

18. I now turn to the prior art cited by the examiner. The examiner cited the following references: Hyon (US 4,663,358), Tanihara (US 5,880,216), Ku (US 5,981,826), Yao (US 6,268,405), Yamauchi (JP 03215417), or Okamura (JP 04338326). These references do not disclose injectable thetagel solutions that form physically crosslinked PVA hydrogels without chemical crosslinkers, irradiation or thermal cycling. More specifically, Ku, Yao, Hyon, and Okamura employ thermal cycling (by freezing) to form a hydrogel. Yamauchi *et al.* employs ionizing ionized radiation to form a gel. Tanihara employs one or more of (a) cross-linking with radiation or peroxides (a chemical crosslinker); (b) cooling the solution; (c) freezing of the solution; and (d) repetition of freezing and thawing. Accordingly, the references alone and in combination do not advantageously use first and second solutions to change the Flory interaction parameter in a controlled manner to allow a hydrogel to form and crosslink over time in a manner that allows it to remain workable. Thus, the skilled person relying on the prior art would not be led to the claimed invention.

19. The claimed invention also unexpectedly satisfies a long felt but unmet need in the field. As explained above, the vertebrate fusion and implanted disk replacements have undesired consequences of loss of motion and deleterious transfer of loads, and require invasive surgeries. Other attempts at injectables employ chemical crosslinkers or are merely phase change materials that lack physical crosslinking by hydrogen bonds or the like. The shortcomings in the field are satisfied only by the claimed invention, which provides and allows for (1) minimally invasive surgery, (2) a porous, highly hydrated system allows fluid and nutrient flow from endplates, (3) space-filling for optimal load-transfer to the annulus fibrosis, (4) the absence of chemical crosslinkers, so there are no unwanted chemical by-products or exothermic (heat) occurrences, and (5) no need for ionizing radiation or thermal cycling, so the hydrogel can form *in situ*, and fill and conform to the body space.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

September 17, 2008

Gavin Braithwaite

Gavin J. C. Braithwaite

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Professional Preparation

Institution and Location	Major/Area	Degree	Date Conferred
Undergraduate			
Edinburgh University, Edinburgh, UK	Physics	B.S.	1992
Graduate			
Southampton University, Southampton, UK	Electronics	M.S	1993
Imperial College of Science, Technology and Medicine, London, UK	Chemical Engineering	Ph.D.	1997
Postdoctoral			
Harvard University	Fluid Mechanics		1997-1998
Massachusetts Institute of Technology	Fluid Mechanics		1998-1999

Research and Professional Experience

2005-Present **Cambridge Polymer Group, Inc.**

Vice-President of Research. Responsible for managing the general research programs within CPG and overseeing all external and longer-term projects. CPG currently has seven research staff. Projects range from basic analytical testing for clients to collaboration on medical devices and materials for Zimmer Inc. and can involve single or multiple personnel. Was responsible for budgeting of the Zimmer deal. This deal involves collaboration with a research laboratory at MGH, out of which a number of patents are currently being filed.

1998-Present **Cambridge Polymer Group, Inc.** Cambridge, MA

Senior consultant. Responsible for surface chemistry and polymeric and colloidal solution properties and blending systems. Expert in rheological analysis, atomic force microscopy, FTIR and DSC. Instrument design and fabrication and software design and development. Designed and built Capillary Break-up Extensional Rheometer (CaBER™). Interested in behavior of polymers in solution and near surfaces and particles. Particular interests include associative and self-assembling systems and biological systems. Principle Investigator (PI) on NSF SBIR phase I and II grants and NIH phase I grant. Responsible for management of entire project, research and personnel and contractors. co-PI on NIH R01 and co-investigator on NASA and NIH R21 grants. Also in overall charge of half of CPGs project load (with Stephen Spiegelberg) and entirely responsible for IT at the company.

1998-1999 **Massachusetts Institute of Technology** Cambridge, MA

Post Doctoral Research Associate with Prof. Gareth McKinley in the Department of Mechanical Engineering. Research included the design and development of a parallel-plate rheometer capable of studying the rheology of polymer melts at plate separations of the order of micrometers. We also examined the effects of blend formulations on the tensile properties of polymer solutions.

1997-1998 **Harvard University** Cambridge, MA

Post Doctoral Research Associate with Prof. Gareth McKinley in the Department of Mechanical Engineering. Research included the design and development of a parallel-plate rheometer capable of studying the rheology of polymer melts at plate separations of the order of micrometers.

1990 and 1991 **National Cash Registers (Dundee), Dundee, UK**

Part of the integration and testing group involved in designing test protocols for, and pre-release testing of, the next generation of Automated Teller Machines used by banks worldwide.

Education

1993-1997 **Imperial College of Science, Technology and Medicine, London, UK**

Research Associate with Prof. Paul Luckham and Dr. Andrew Howe. PhD research project in Chemical Engineering involved examination and understanding of inter-particle forces in sterically stabilised colloidal systems. Constructed a custom Atomic Force Microscope (AFM) for normal force spectroscopy of a solvated polymer layer. Studied poly (ethylene oxide) adsorbed to silica in water, and also worked on gelatine under various solution conditions and the possibility of extending the apparatus to examine dynamic micro-rheological properties. Also used Total Internal Reflection Fluorescence (TIRF) to study polymer kinetics near surfaces. Partially funded through grant from Kodak UK.

1992-1993 **Southampton University, Southampton, UK**

MSc in Electronics: Final project "Digital Baseband Processing of PI/4 QPSK Signals" and involved the coding of a digital implementation for PI/4 QPSK differentially coherent demodulation. This was intended for a packet switched radio network (for use in low cost digital field telephones in Africa).

1988-1992 **Edinburgh University, Edinburgh, UK**

BSc in Physics: Final year projects were "Resonance in pipes (clarinet)" (with Dr. M Campbell) and "Colloid Rheology - non-Newtonian Flow" using the settling of particles in a medium (with Prof. P.N. Pusey and Dr. W.C.K. Poon). Optional modules included Acoustics and Fluid Dynamics, Advanced Quantum Theory, Solid State Physics, Fluid Dynamics, Lasers and Techniques of Scientific Computing and completed part of the B.Eng in Electrical Engineering.

SOCIETIES AND ORGANIZATIONS

Institute of Physics
American Physical Society
The Society of Rheology
American Chemical Society
Spine Arthroplasty Society

GRANTS

NIH

PI

SBIR phase I (1R43 CA 90163-01) A novel, fast, reliable and inexpensive radiation dosimeter (2001)

Co-PI

SBIR phase I (1 R43 EY14280-01) A Method to Generate Artificial Cornea Constructs (2004)

R01 Engineering Biomimetic corneal constructs (2005) – since transferred to North Eastern University

Sub-contract

R21 Biopolymer injection to prevent Mitral regurgitation (2006) with MGH cardiovascular research laboratory

NSF

PI

SBIR phase I (DMI-0132046) A novel instrument for the determination of extensional rheology (2001)

SBIR phase II (DMI-0132046) A novel instrument for the determination of extensional rheology (2002)

Co-PI

SBIR phase I (DMI-0060427) Instrument for swelling measurements of crosslinked polymers (2000)

NASA

Sub-contractor

SBIR phase II Multiple configuration spacecraft environment (2002)

Publications and Presentations

Thesis:

G.J.C. Braithwaite (1997), "Colloidal Interactions Measured Using a Modified Force Microscope" In *Chemical Engineering* Imperial College of Science Technology and Medicine, London University, London, pp. 311.

Peer-reviewed

1. J. S. Colton, G. J. C. Braithwaite, B. J. Briscoe and P. F. Luckham (1995) In *19th Annual Meeting of the Adhesion Society* Myrtle Beach, pp. 331-334.

2. J. S. Colton, G. Braithwaite, B. J. Briscoe and P. F. Luckham (1996) In *11th Technical Conference, American Society for Composites* Atlanta, pp. 797-801.

3. G. J. C. Braithwaite, P. F. Luckham and A. M. Howe (1996) "Interactions between Poly(ethylenoxide) layers adsorbed to glass surfaces probed by using a modified AFM", *Langmuir*, **12**, 4224-4237.

4. G. J. C. Braithwaite and P. F. Luckham (1997) "Effect of Molecular Weight on the Interactions between Poly(ethylene Oxide) Layers adsorbed to Glass Surfaces", *Journal of the Chemical Society, Faraday Transactions*, **93**, 1409-1415.

5. P. F. Luckham, G. J. C. Braithwaite and A. Howe (1997) "Interactions between adsorbed gelatin layers", *Imaging Science Journal*, **45**, 223.

6. P. F. Luckham, G. J. C. Braithwaite and R. Nowakowski (1998) In *Abstracts of Papers of the American Chemical Society 215th Conference*, Vol. 1, April 2nd Dallas, TX, pp. U432-U432.

7. G.J.C. Braithwaite and G. H. McKinley (1998) In *Abstracts of Papers of the American Chemical Society 215th Conference*, Vol. Part 1, April 2nd Dallas, TX, pp. U485-U485.

8. G. J. C. Braithwaite, P. F. Luckham, and A. Howe (1999) "Study of a solvated adsorbed gelatin layer using a modified force microscope" *Journal of Colloid and Interface Science*, **213**, 1, 525-545.

9. G. J. C. Braithwaite and P. F. Luckham (1998) "The Simultaneous Determination of the Forces and Viscoelastic Properties of Adsorbed Polymer Layers", *Journal of Colloid and Interface Science*, **218**, 1, 97-111

10. G. J. C. Braithwaite and G. H. McKinley (1999) "Microrheometry for Studying the Rheology and Dynamics of Polymers near Interfaces" *Journal of Applied Rheology*, **9**, 27-33.

11. H. Bodugoz-Senturk, J. Choi, E. Oral, J.H. Kung, C.E. Macias, G. Braithwaite and O.K. Muratoglu (2008) "The effect of polyethylene glycol on the stability of pores in polyvinyl alcohol hydrogels during annealing", *Biomaterials* **29**, 2, 141-149

BOOKS

1. G. J. C. Braithwaite and P. F. Luckham (1996) "Study of Attractive Interactions between Poly (Ethylene Oxide) Coated Surfaces Using AFM" In *Micro/Nanotribology and its applications* (Ed, Bhushan, B.) Kluwer Academic Publishers, Dordrecht.

2. G. Braithwaite, P. Luckham, A. Meurk and K. Smith (1997) "Probing Colloidal Interactions Using Modified Atomic Force Microscopy" In *Modern Aspects of Colloidal Dispersions: Results from the DTI Colloid Technology Programme* (Eds, Ottewill, R. H. and Rennie, A. R.) Kluwer Academic Publishers, Dordrecht.

PATENTS

1. Device and Method for measuring extensional rheological properties of materials. Braithwaite, McKinley and Spiegelberg (US 6,711,941)

2. System and methods for reducing interfacial porosity in cements. Spiegelberg, Ruberti and Braithwaite (US 6,884,264)

3. System and methods of controlling and forming polymer gels. Ruberti and Braithwaite (filed 2002)

4. Layered aligned polymer structures and methods of making same. Braithwaite and Ruberti (US 7,048,963)

5. Tough hydrogels. Muratoglu, Choi, Senturk, Braithwaite, Spiegelberg (provisional filed 2005)

CONFERENCE PRESENTATIONS

1. 69th ACS Colloids and Surfaces Science Symposium (with P.F. Luckham and A. Howe), Salt Lake City UT, USA. (1995)

2. 3rd SCI UK Colloid and Surface Science Student Meeting (with P.F. Luckham), Hull, UK (1995)

3. 71st ACS Colloids and Surfaces Science Symposium (with P.F. Luckham and A. Howe), Newark DE, USA (1997) - 1

4. 71st ACS Colloids and Surfaces Science Symposium (with P.F. Luckham and A. Howe), Newark DE, USA (1997) - 2

5. 215th ACS National Meeting, (with G. McKinley), Dallas TX, USA (1998)

6. Mechanics of Nonlinear Materials (with G.H. McKinley), Banff, Canada (1998)

7. 71st Annual Meeting Society of Rheology (with G.H. McKinley), Madison, Wisconsin, USA (1999)

8. 72nd Annual Meeting Society of Rheology (with S.H. Spiegelberg), Hilton Head, South Carolina, USA (2001)

9. 30th American Chemical Society New England Regional Meeting (with S.H. Spiegelberg), Durham, New Hampshire, USA (2001)

10. Neal, G. and Braithwaite, G. *The use of Capillary Breakup Extensional Rheology to examine concentration dependence of relaxation time*. in *Society of Rheology Annual Meeting*. 2003. Pittsburgh, PA.

11. Melotti, G., Fudge, D., and Braithwaite, G. *The use of Capillary Breakup Extensional Rheology to examine concentration dependence of relaxation time*. in *Society of Rheology Annual Meeting*. 2003. Pittsburgh, PA.

12. Society for Biomaterials 2005 Annual Meeting (with BR Burroughs, GM Neal and OK Muratoglu), Memphis, TN, USA (2005)

CONFERENCE POSTERS

1. NATO ASI Micro/Nanotribology and its Applications, Sesimbra, Portugal. (1996)

2. 3rd EPS Liquid Matter Conference, Norwich, UK. (1996)

3. 70th Annual Society of Rheology Meeting, Monterey, USA (1998)

4. Spine Arthroplasty Society, New York, USA (2005)

5. Spine Arthroplasty Society, Miami, USA (2008)

Invited Speaker

1. Institute of Surface Chemistry, Stockholm, Sweden. (1995)

2. Burleigh Instruments SPM Users Meeting., Loughborough, UK. (1996)

3. School of Mechanical Engineering, Georgia Institute of Technology, Atlanta GA, USA. (1996)

4. Keynote speaker at Rheofuture (2004), Karlsruhe, Germany

5. Plenary Lecture, New England Biomedical Engineering Conference, Brown University, Providence RI (2008)

SYNERGISTIC ACTIVITIES

Dr. Braithwaite organized an undergraduate research project at MIT to teach students new techniques in extensional rheometry, and in characterizing polymeric fluids in general.

COLLABORATORS

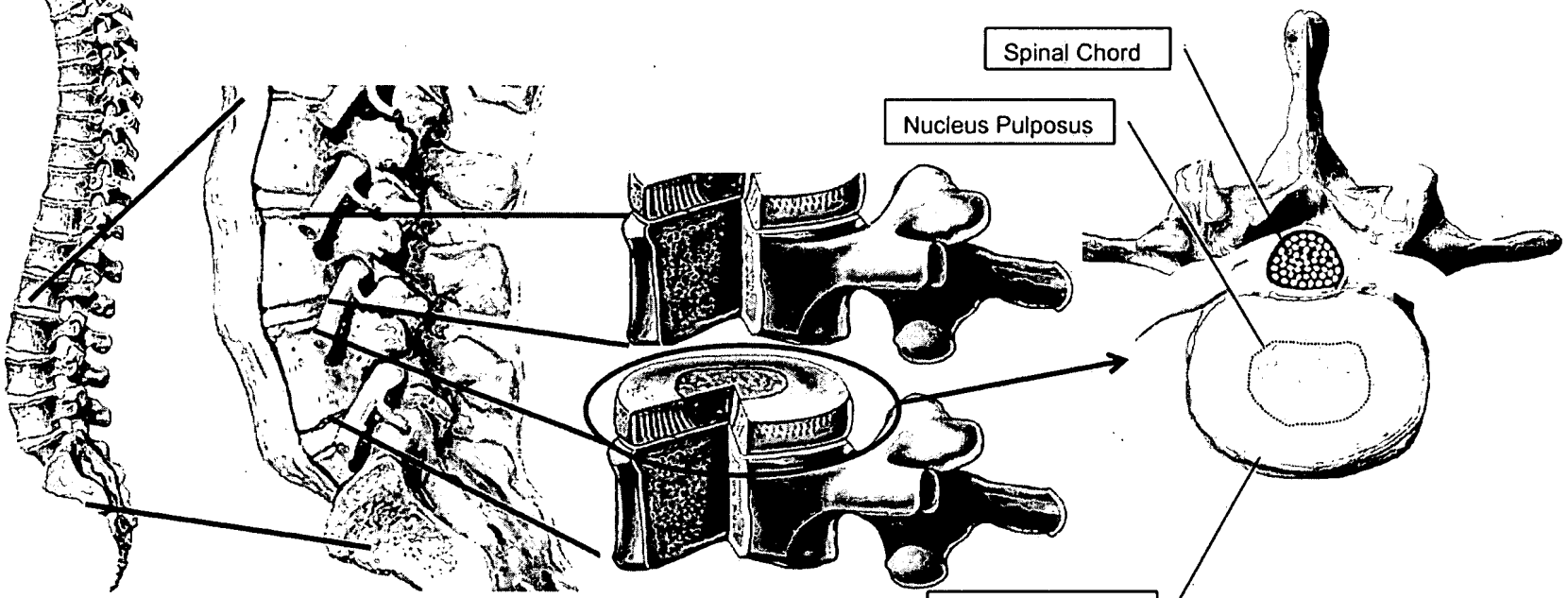
Professor Brian Briscoe, Imperial College
Professor Jonathon Colton, Georgia Institute of Technology
Dr. Andrew Howe, Kodak European Research
Professor Paul Luckham, Imperial College
Professor Gareth McKinley, Massachusetts Institute of Technology
Dr. Anders Meurk, Institute of Surface Chemistry, Stockholm
Dr. Robert Nowakowski
Dr. Kate Smith

GRADUATE AND POSTDOCTORAL ADVISORS

Mr. Steve Braithwaite, Southampton University
Prof. Brian Briscoe, Imperial College
Dr. Andrew Howe, Kodak European Research
Professor Paul Luckham, Imperial College

Spine and Disc Structure

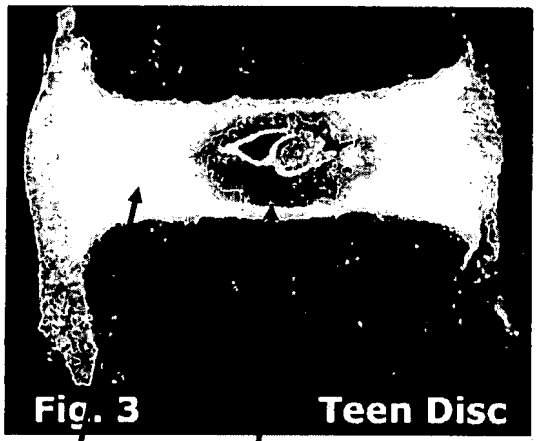
The spine is a column of boney blocks (the vertebrae) joined by collagenous, flexible spacers (intervertebral discs). The intervertebral discs are fibrocartilaginous cushions serving as the spine's shock absorbing system, which protect the vertebrae, brain, and other structures (i.e. nerves). The discs allow some vertebral motion: extension and flexion. Individual disc movement is very limited – however considerable motion is possible when several discs act in concert.

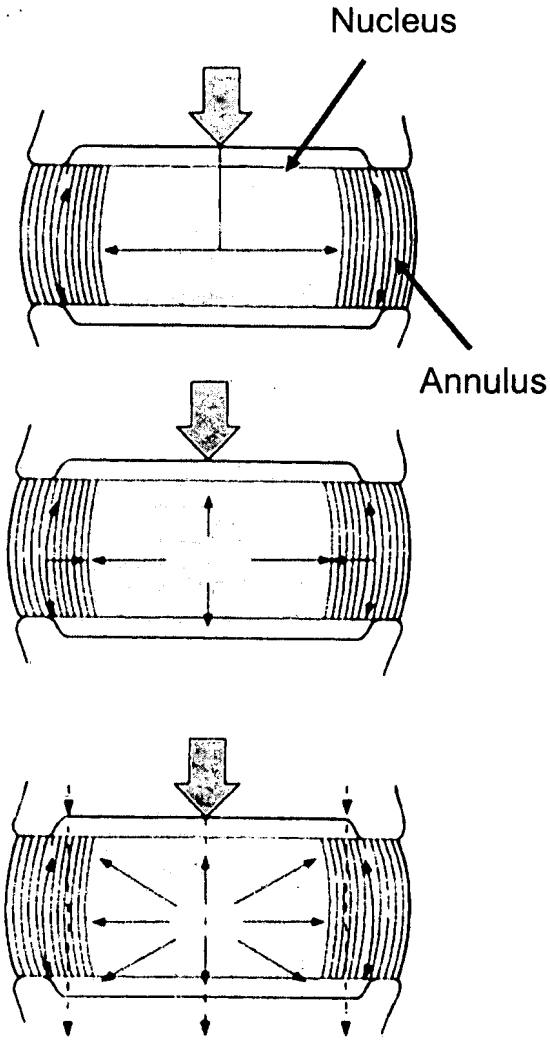


Images: http://www.backpain-guide.com; http://www.eorthopod.com

Disc Mechanics

- The healthy disc is a composite structure of annulus fibrosus and nucleus pulposus
- This structure allows weight distribution and flexibility

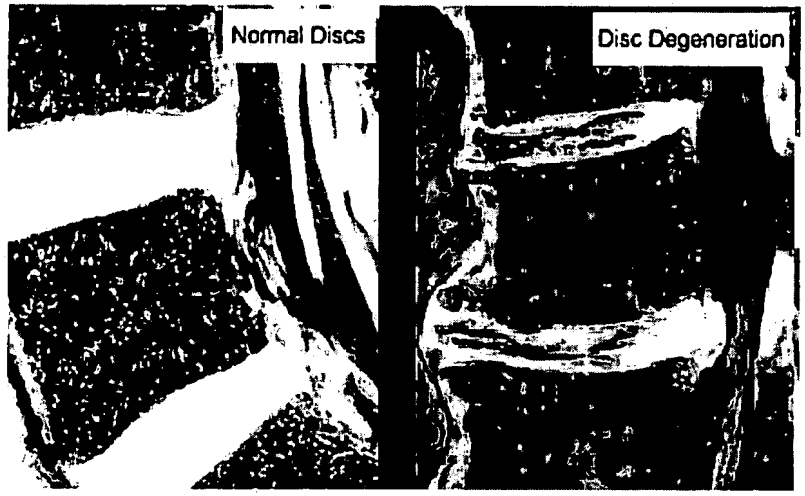




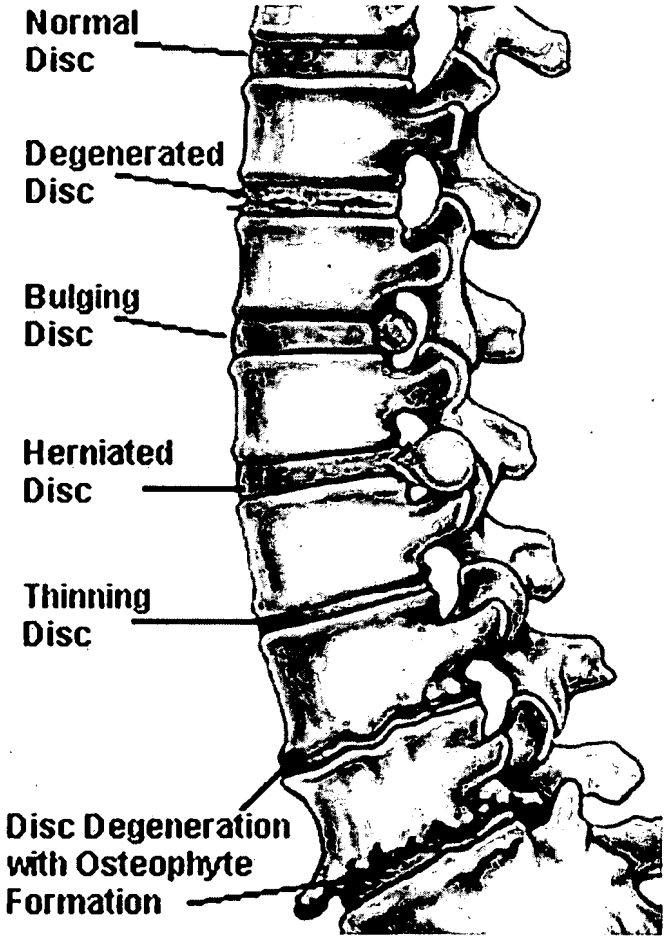
www.chirogeek.com; Bogduk, N., *Clinical Anatomy of the Lumbar spine and Sacrum*

Degeneration of the human spine

- A range of issues cause problems in the spine and result in pain
- Loss of height through degeneration or trauma is a prime cause
- Loss of water from the disc also changes biomechanics
- All result in pain or loss of mobility

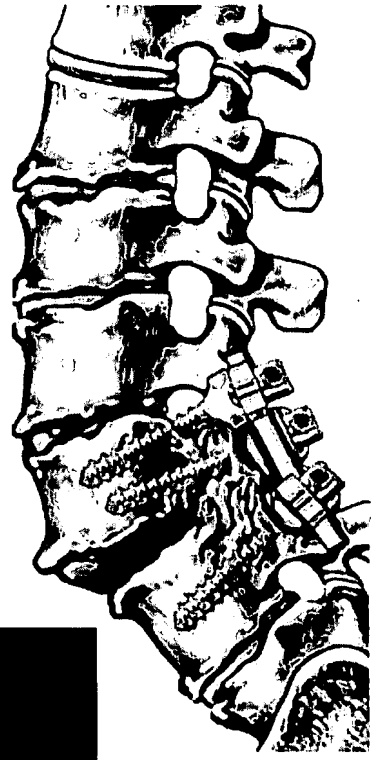


www.chirogeek.com

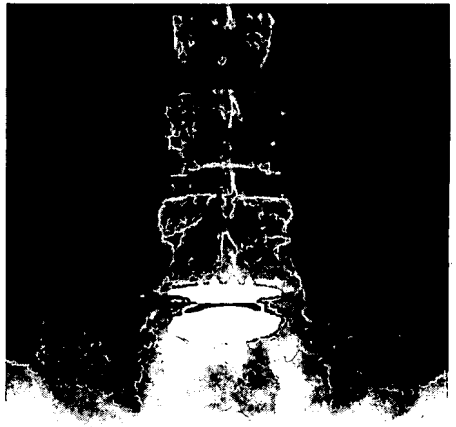


www.spineuniverse.com

Current Treatment



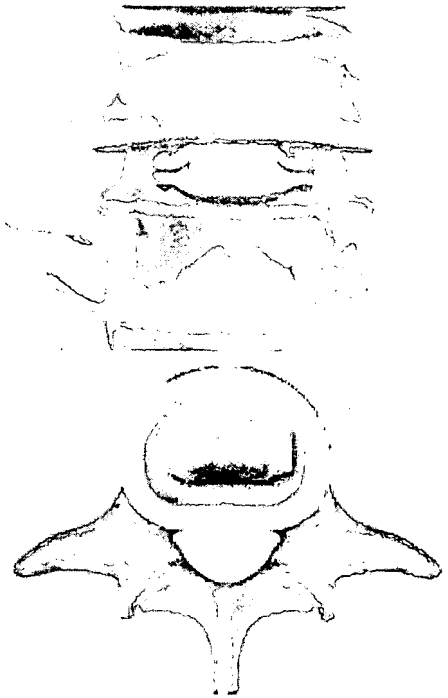
- Fusion
  - "locks" affected joint in place
  - Prevents "motion" to reduce pain
  - Permanent and invasive
  - Successful
- Total disc replacement
  - "replaces" joint with biomechanical construct
  - Preserves motion
  - Permanent and very invasive
  - True success rate unknown



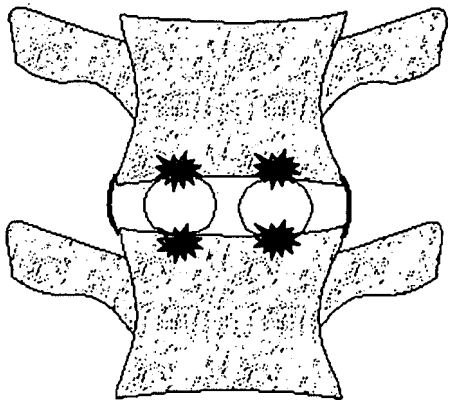
Healthlibrary.ep.net; www.spine-health.com; www.worldmedassist.com

Next-generation Treatment (Raymedica)

The Raymedica device is implanted partially collapsed, through an incision smaller than the eventual device, but still large relative to the disc space. This incision must be repaired by the surgeon. Early examples of the device were seen to expel through the incision.



A three-dimensional solid object cannot fully fill the space it is inserted into, running the risk of unevenly loading the disk. The Raymedica device has suffered from "end-plate subsidence" in the past.



medgadget.com

Newest concepts - Injectables

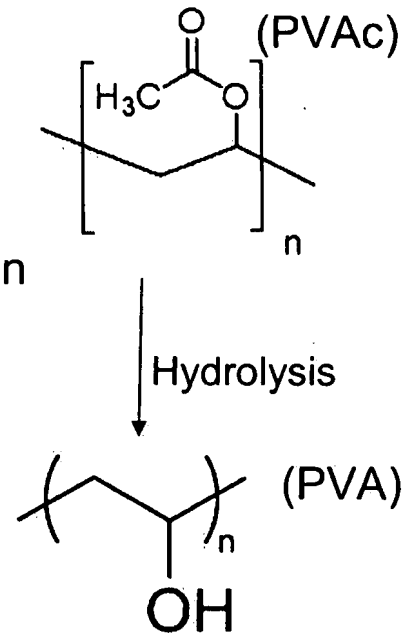
Device	Company	System	Ref	Crosslinker
BST-Disc	BioSyntech	Chitosan-based gel using glycerol phosphate to form a thermodynamic gel	1,2	Thermodynamic (LCST)
Gelifex IP	Synthes	poly(N-isopropylacrylamide) (PNIPAAm) copolymer with PEG	9	Thermodynamic (LCST)
Dascor	Disc Dynamics	Rubber formed with aliphatic polycarbonate-based polyurethane balloon filled with oligo-urethane units formed from diisocyanate and chain extender with soft segments comprised of polyol units.	3	Chemical (isocyanate)
Sinux ANR	DePuy (J&J)	Elastomer platinum catalyzed poly(methylsiloxane)	4	Chemical (PMSO)
PNR or PDR	TranS1	Silicone elastomer	5	Chemical (PMSO?)
Biodisk	Cryolife	Hydrogel formed from a mixture of human or animal-derived protein at 27-53% and a di- or polyaldehyde crosslinker at about 1 part to 20-60 parts of protein	6	Chemical (aldehyde)
	Biocure	Hydrogels formed from macromers having a poly(vinyl alcohol) backbone comprising units with a 1,2-diol or 1,3-diol structure and at least two pendant chains and an acrylamide comonomer.	7	Chemical (NAAADA)
DiscCell	Gentis	Polymerizable emulsion is a water-in-oil emulsion composed of lauryl acrylate monomer with PE-PEO surfactant, HLV plus water. Organic phase is ethylenically unsaturated monomers or oligomers.	8	Chemical (BApO)
NuCore IDN	Spinewave	Synthetic silk-elastin copolymer with a chemical structure of two silk and eight elastin blocks per repeat.	10	Chemical (lysine/cyanate)

1 Chenite US 7,098,194 (2006);
2 http://www.biosyntech.com/en/expertise/orthopedics/?BST=Disc;
3 Bao US 7,001,431 (2006);
4 Zollner US 6,520,922;
5 www.nucleusarthroplasty.com/media/biomechanics/chapter8.pdf;
6 Kowanko US 5,385,606;
7 Chaouk US20050288789A1;
8 Devore US20050112186;
9 Thomas, D. J., et al. In *Synthesis and Characterization of Injectable Bioresponsive Hydrogels for Soft Tissue Replacement*, 52nd Annual Meeting of the Orthopaedic Research Society, Chicago, IL, 2006;
10 Nettles, D. L., et al. In *Injectable Silk-Elastin for Articular Cartilage Defect Repair*, 51st Annual Meeting of the Orthopaedic Research Society, Washington, DC, 2005;

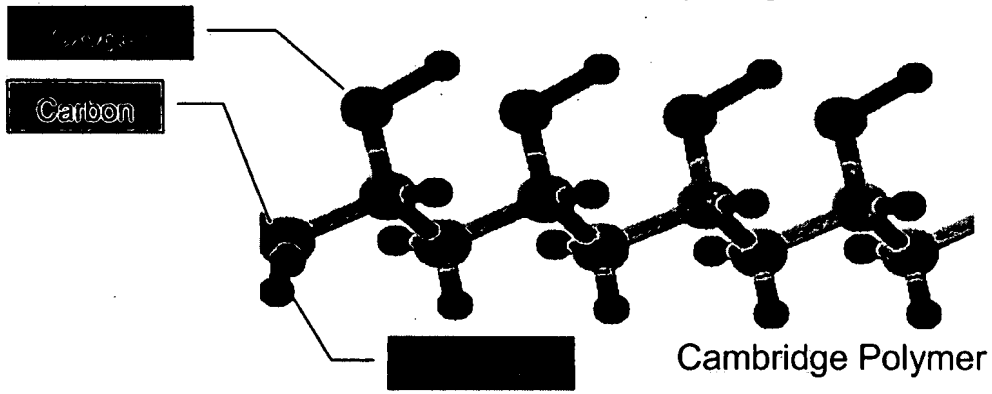
However..

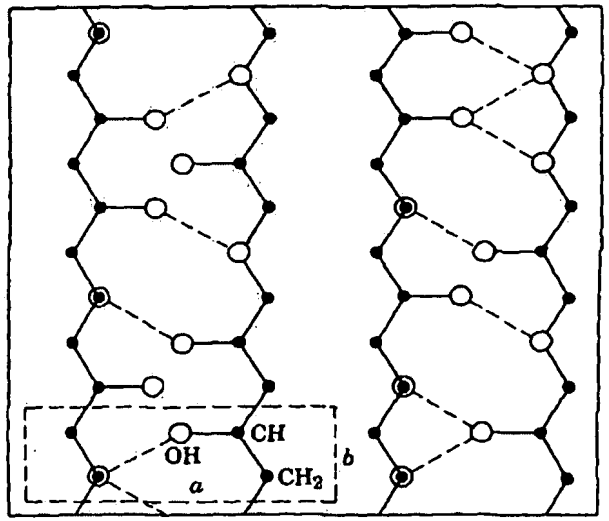
- The problem with all other current injectable systems is that they either:
  - require chemical crosslinkers
  - use new or unusual polymers that can be susceptible to degradation
  - are likely to be complex to manufacture
  - are "phase change" materials that really solely on associative forces (no bonding) to maintain integrity
- There is therefore a need for a proven polymer-based hydrogel that can be administered in an injectable fashion
- Poly(vinyl alcohol) is a proven biomaterial
  - Cartilage, nerve cuffs - Salumedica - http://www.salumedica.com/
  - Foam embollization spheres - Cook Medical – www.cookmedical.com
  - Embollization microspheres - Boston Scientific – www.bostonscientific.com
  - Contact lens lubricants – Alcon – www.alcon.com

Poly(vinyl alcohol)



- Poly(vinyl alcohol) (PVA) is
  - A chain of carbons with alternating hydrogen and oxygen
  - Highly hydrophilic (water loving)
  - Easily made by hydrolysis of poly(vinyl acetate) (PVAc)
  - Used in solid biomedically
- The polymer is
  - A simple hydrocarbon chain with pendant hydroxyl groups
  - Structure is similar to poly(ethylene)
    - CHOH group fits into CH_2 structure
    - *Chains can link via hydrogen bonds into sheets*





Polymer thermodynamics

- When a molecule is mixed with a solvent how the system behaves depends on two basic parameters:
  - The Entropy of Mixing that describes the energy released by "disordering" the molecules
    - In the case of polymers this can be very complex due to their unique shapes
  - The Heat of Mixing that describes the energy gained or lost to force two dissimilar molecules together
- The free energy of mixing of a solution is the difference between the energy expended in making the solution (heat of mixing) and the energy returned by the increase in disorder of the system (entropy of mixing):

$$\Delta F = \Delta H - T\Delta S$$

$$= kT\left[n_1 \ln v_1 + n_2 \ln v_2 + \chi_1 n_1 v_2\right]$$

- Where v_1 and v_2 are the respective volume fractions of the components and n_1 and n_2 are the number of molecules present

χ_1, is the Flory Interaction parameter

$$\chi_1 = \frac{z\Delta w_{12} x_1}{kT}$$

The Flory Interaction Parameter

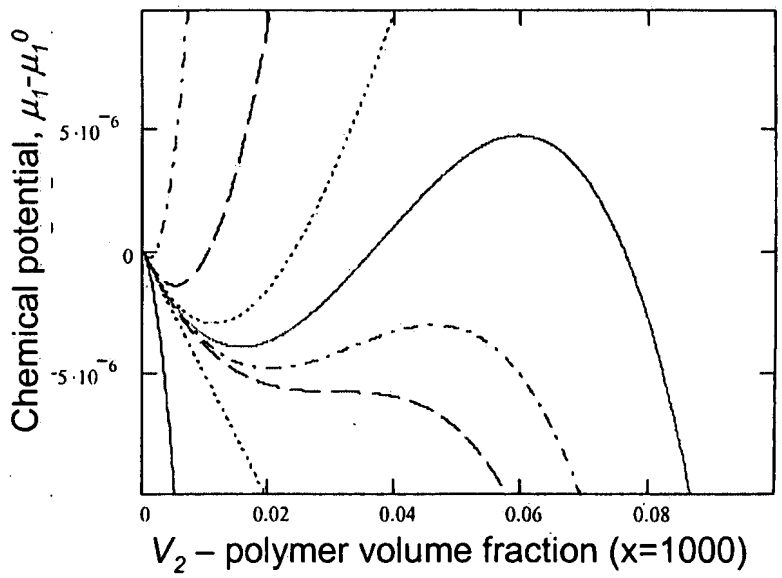
- The chemical potential of the solvent in the solution describes how the energy of the system changes per molecule added with all other parameters held constant:

$$\mu_1 - \mu_1^0 = RT\left[\ln(1-v_2) + \left(1-\frac{1}{x}\right)v_2 + \chi_1 v_2^{\,2}\right]$$

- Which only depends on v_2 (polymer volume fraction), x (polymer length) and χ_1, the Flory Interaction parameter and is linked to the solvent "activity", a_1.

$$\mu_1 - \mu_1^{\,0} = RT\ln a_1$$

- A molecule is only soluble if the free energy results in a positive chemical potential



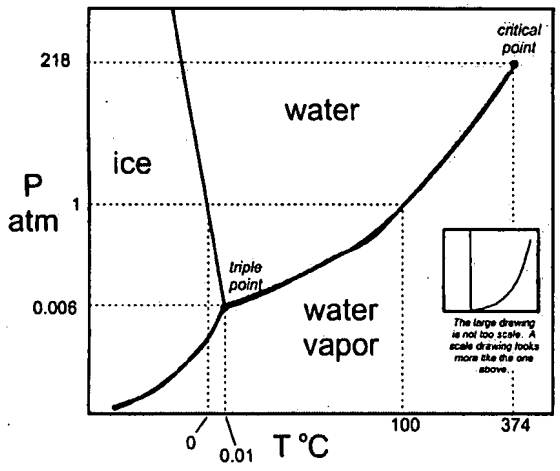
Polymer chains in solution

- The condition where χ_1=0.5 is known as a theta solvent. According to Wikipedia, a theta solvent (or θ solvent) is a solvent in which polymer coils act like ideal chains, assuming exactly their random walk coil dimensions. Thermodynamically, the excess chemical potential of mixing between a polymer and a theta solvent is zero.
- A Flory theta solvent neither extends nor contracts the coil of a polymer chain. A theta solvent is between a "good" solvent and a "poor" solvent
  - A “good” solvent extends the polymer chains and makes it soluble
  - A "poor" solvent contracts the polymer chain and makes it insoluble

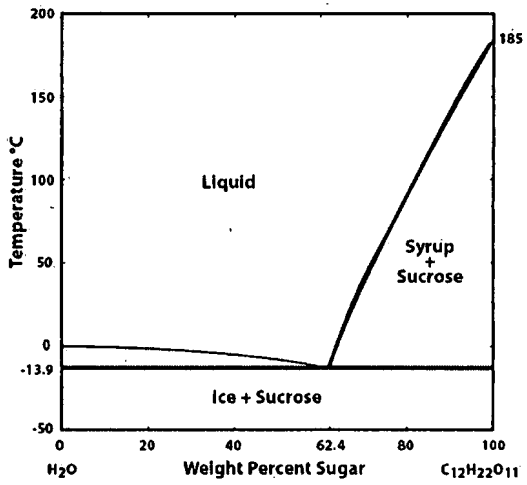
Phase Diagram

- Any material or combination of materials exhibits a phase diagram
- The phase diagram describes what external influences, such as temperature, pressure and concentration govern the system
- The solvent also governs the phase diagram

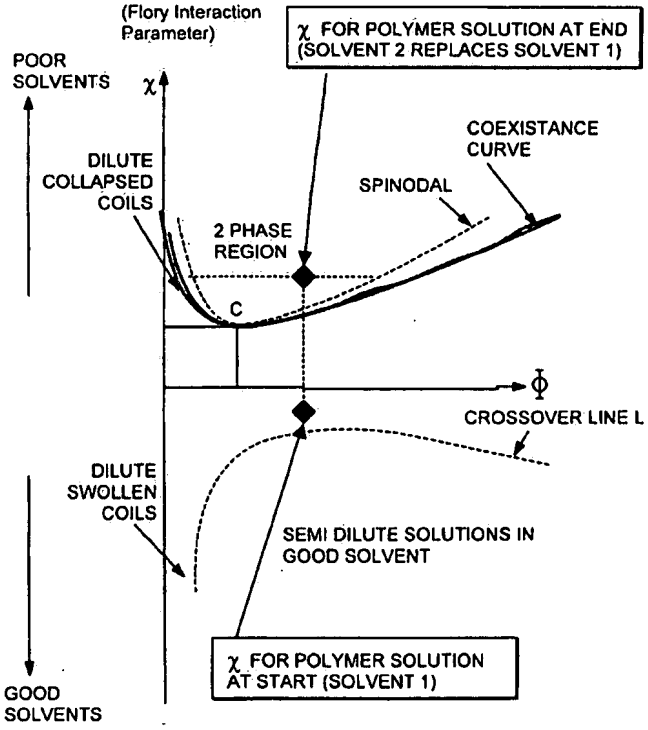
Single species phase diagram (water)



Binary phase diagram (water/sucrose)



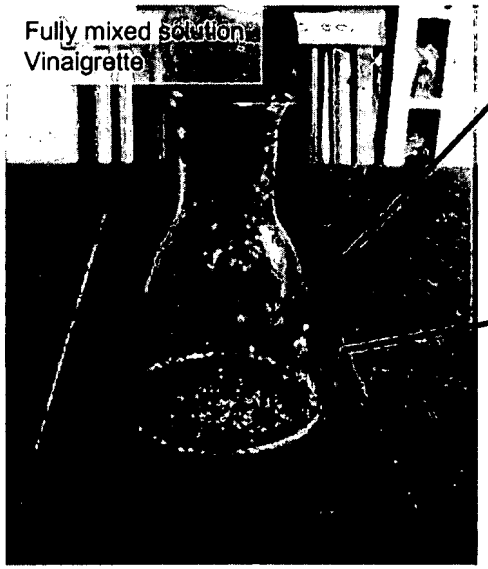
Binary phase diagram (polymer/solvent)
Or
Ternary phase diagram (water/polymer/gellant)

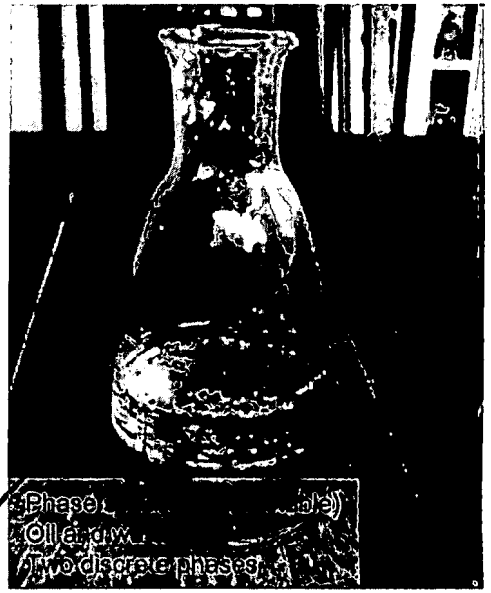


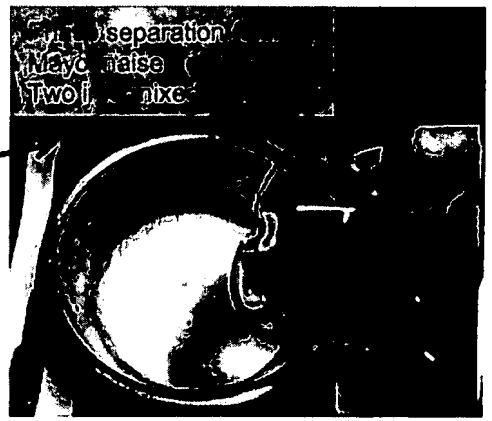
http://serc.carleton.edu

Phase Separation

- Phase Separation results in two components coexisting along side each other
  - Stable (Mayonnaise) fat globules indefinitely separated homogeneously at the microscopic level from the water
  - Unstable (Vinaigrette) fat globules coalesce and macroscopically separate

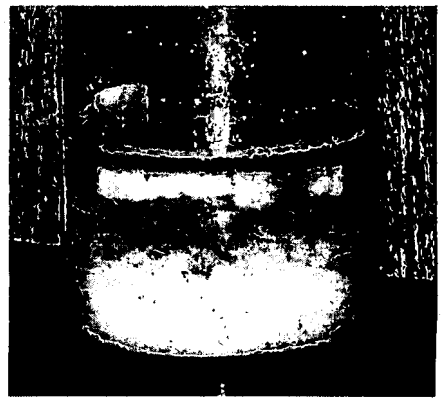


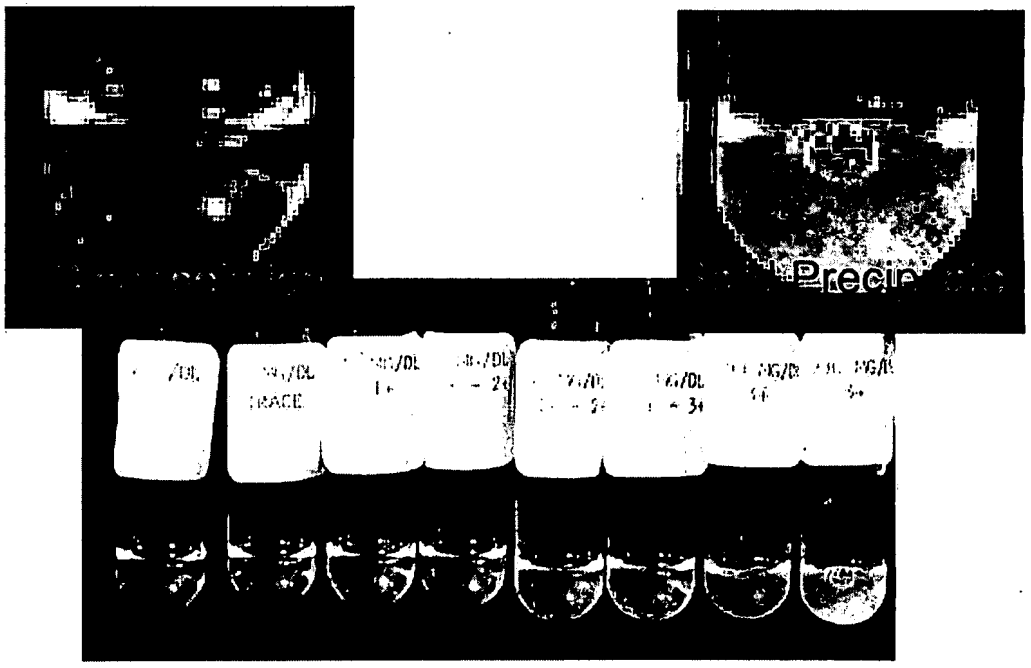




Precipitation

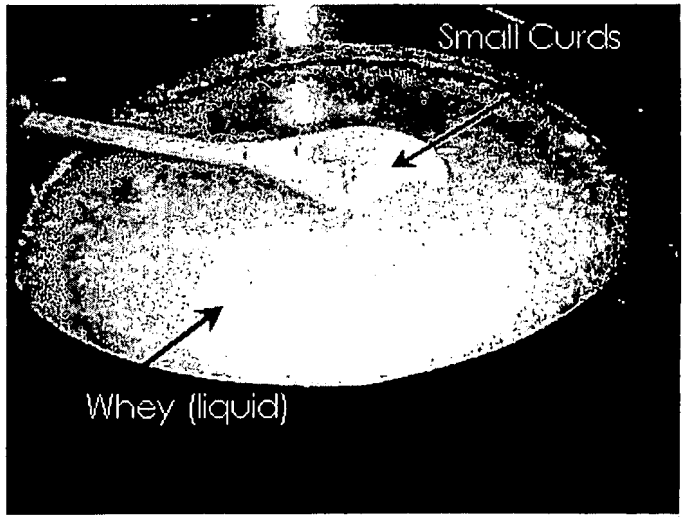
- Precipitation ("crashing out") occurs when solution conditions no longer allow one of the ingredients to remain dissolved.
- In protein separation this is referred to as "salting-out" and is driven by excess salt.





Polymer solutions and solvents

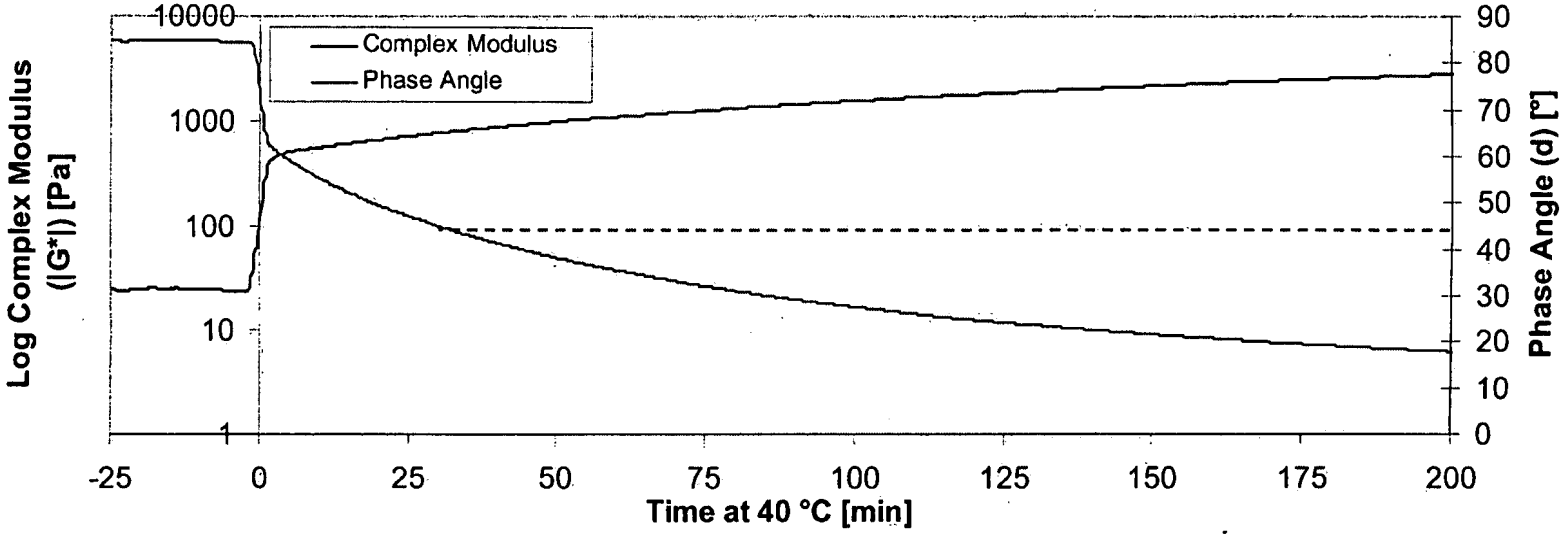
- A polymer solution is formed where the polymer is completely compatible at the molecular level with the solvent
  - Milk (of all types) is an example with casein (milk proteins – a natural polymer) freely suspended in the whey
- If the solution conditions change then the polymer may no long be soluble
  - When vinegar is added to milk it curdles because the casein is no longer soluble and coagulates together forming a precipitate – this is how cheese curds are made



www.deejayssmokepit.net/

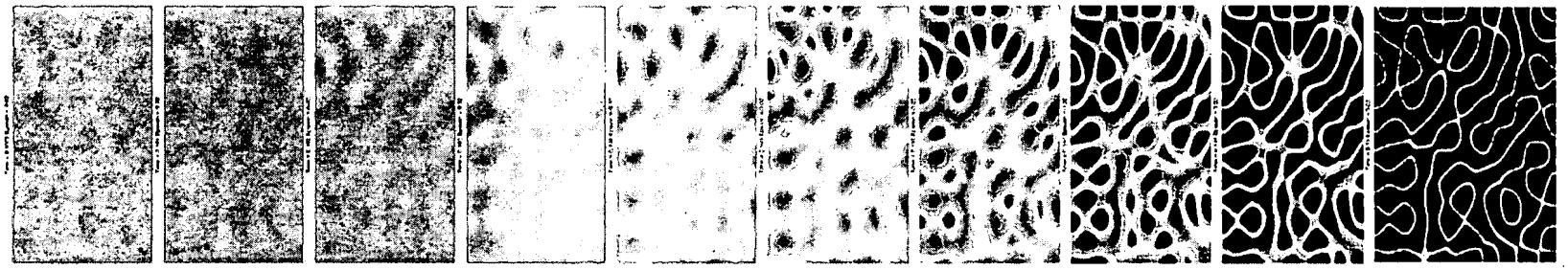
Workability (injectability)

- The phase separation takes time to evolve



Homogeneous

Separated



TIME

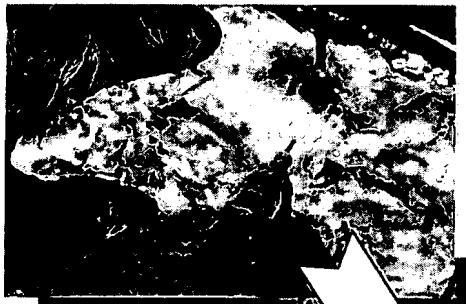
Gelation of poly(vinyl alcohol)

- PVA is unique in that it permanently gels through a phase separation and physical crosslink process
- Other polymers will exhibit a phase-transition as outlined above if the conditions are right, separating into polymer-rich and polymer-poor phases. These polymer-rich regions are thermodynamically favourable
  - Ultimately they make the polymers "sticky", preferring the polymer to the solvent
  - There is no "bond" per se
  - Thus the structure is transient and can be broken
  - The Gelifex and BST-Disc are examples of these kinds of systems
- Poly(vinyl alcohol) undergoes the same separation but
  - The physical crosslinks (hydrogen bonds) are permanent
  - Once formed these bonds are stable

Injectable and biocompatible

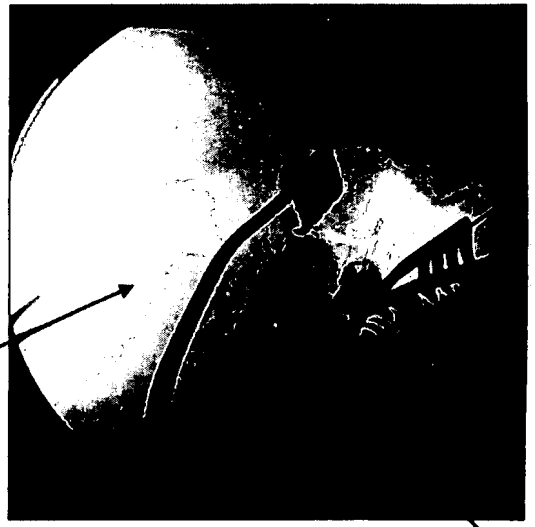
- By controlling the addition of a tertiary ingredient (the "gellant") the gelation time can be controlled, thus the pre-gel (liquid thetagel) can be injected or handled before the material has gelled, without interrupting the gelation
- By choosing a biocompatible gellant, PVA hydrogels are rendered injectable and biocompatible
  - This biocompatible agent can be any molecule that manipulates the flory interaction parameter of the PVA
    - E.g. poly(ethylene glycol), common salt, chondroitin sulfate etc etc

Surgical Procedure



Surgical injection through needle

Porcine animal model proof-of-concept



Syringe and needle

Interoperative fluoroscopy

Hydrogel in disc

Implant conforms to shape of the nucleus

Injection of a biocompatible PVA hydrogel